Rule 126 76-77. The antibody of claim 1, wherein said antibody comprises a variable heavy (VH) complementarity determining region (CDR) listed in Table 4 (nucleotides 31-35, 50-66, or 99-114 of any one of SEQ ID NOS:51-74). --

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Status of the Claims.

Claims 1-43 and 77 are pending with entry of this amendment, no claims being cancelled and claim 77 being added herein. Claims 6-10, 17-29, and 36-42 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification and, in particular, is found in Table 4.

35 U.S.C. §112, Second Paragraph.

The rejection of claims 6-10, and 17-43, under 35 U.S.C. §112, second paragraph, as allegedly indefinite for using the terms "variable heavy complementarily [sic] determining regions (CDRs) listed in Table 4", "variable light complementarily [sic] determining regions (CDRs) listed in Table 4", framework region listed in Table 4" and "the antibody of claim1" was maintained. IN particular the Examiner alleged that absent express reference to sequence ID numbers, the cited language was indefinite.

Although Applicants believe the Examiner's position is legally incorrect, to expedite prosecution, the claims are amended to recite particular sequence ID numbers thereby obviating this rejection. Applicants note, for the record, that this amendment does not narrow the scope of the claimed invention.

With respect to the rejection of claim 17 because of its recitation of "the antibody of claim1" Applicants respectfully submit that the Examiner has misread claim 1. Contrary to the Examiner's assertion, claim 1 **does not** claim two different antibodies (an isolated antibody and an

antibody expressed by a clone). Rather, claim 1 is drawn to antibodies that binds particular epitopes. Those epitopes are defined by reference to the antibodies expressed by the recited clones.

The Examiner's position is simply incorrect and supported by a fallacious reading of claim 1. Accordingly the rejection of claim 17 under 35 U.S.C. §112, second paragraph, should be withdrawn.

35 U.S.C. §102.

35 U.S.C. §102(b).

The rejection of claims 1-11, 13-14, 17-30, 32-33, 36-43 under 35 U.S.C. §102(b) as allegedly anticipated by Atassi *et al.* (1996) *J. Prot. Chem.,* 15(7): 691-699) was maintained. Applicants respectfully traverse.

The Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.,* 218 USPQ 781, 789 (Fed. Cir. 1983). In the instant case, independent claims 1 and 24 are amended herein to recite:

> "1. An isolated **single-chain** antibody. . ."; and
>
> "24. An isolated **single chain** anti-botulinum neurotoxin type A (anti-BoNT/A) antibody. . . "

respectively. In contrast, Atassi, *et al.* only discloses the creation of native (*i.e.,* double-chain) antibodies. Thus, for example, Atassi *et al.* states:

> Horse antisera were prepared by immunization subcutaneously in multiple sites and every 2 weeks for over 1 year, with a formaldehyde inactivated BoNT/A in Biri adjuvant. (Atassi *et al.* page 693, col. 1)
>
> * * *
>
> Human antisera were made against the pentavalent toxoid in human volunteers as described . . . (Atassi *et al.* page 693, col. 1)

Atassi *et al.* offers no teaching whatsoever of a single-chain antibody directed against a botulinum neurotoxin. Accordingly, Atassi *et al.* fails to disclose a limitation of the presently claimed invention

and therefore does not anticipate this invention. Accordingly, the rejection under 35 U.S.C. §102(b) should be withdrawn.

The Examiner alleged that "each of the single chains of Atassi's "native" antibody meets the limitations of the claims, e.g. it specifically binds to an epitope of butulinum neurotoxin type A (BoNT/A) and it can be used in a passive immunity/neutralizing against the toxin poisoning, because they both contain variable region which can specifically bind to an epitope". **The Examiner's position is at best idle speculation and fails to meet the requirements of a proper rejection under 35 U.S.C. §102:**

1) **It is well accepted in the art that a "native" full antibody is not the same as a single chain antibody;** Thus, it is improper to equate the full "native" antibody taught by Atassi *et al.* with a single-chain antibody;
2) **The Examiner has offered no objective teaching establishing that if the two chains comprising the Atassi antibody were separated that either alone would be able to specifically bind to BoNT/A.** Moreover, even even **assuming**, arguendo that the chains could bind BoNT/A, the Examienr has identified no objective teaching establishing that they would bind to the same epitope recited in the present claim.

Lacking any objective evidence, Applicants understand the Examiner's position to be based on personal knowledge and belief. **Accordingly, should the Examiner wish to maintain this position, Applicants request the Examiner to provide an affidavit to this effect as required by 37 C.F.R. 1.107 (see M.P.E.P. 2144.03).**

In view of the foregoing, Applicants believe the Examiner has not made a proper *prima facie* case under 35 U.S.C. §102(b) and, accordingly, this rejection should be withdrawn.

35 U.S.C. §102(a).

The rejection of claims 1-43 were under 35 U.S.C. §102(a) as allegedly anticipated by Amersdorfer *et al.* (1997) *Infect. Immun.*, 65(9): 3743-3752, was maintained.

According to MPEP §2132.01:

> Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982) (discussed below). Therefore, where the applicant is one of the co-authors of a publication cited against his or her application, the publication may be removed as a reference by the filing of affidavits made out by the other authors establishing that the relevant portions of the publication originated with, or were obtained from, applicant. Such affidavits are called disclaiming affidavits. Ex parte Hirschler, 110 USPQ 384 (Bd. App. 1952). **The rejection can also be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work**. In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). [emphasis added]

In the instant case, upon a showing of otherwise allowable subject matter, Applicants will provide Declarations in accordance with *In re Katz*, signed by the inventors of the present application, establishing that the Amersdorfer *et al.* articles describes Applicants' own work.

35 U.S.C. §103(a).

The rejection of 1-43 were under 35 U.S.C. §103(a) as allegedly obvious in light of Atassi *et al.* (1996) *J. Prot. Chem.*, 15(7): 691-699 taken with Emanuel *et al.* (1996) *J. Immunol. Meth.*, 193: 189-197 was maintained. According to the Examiner, while Atassi *et al.* allegedly teaches intact "native" anti-botulinum neurotoxin type A antibodies (anti-BoNT/A) they do not teach or suggest a single-chain antibody. Emanuel *et al.* is cited as allegedly teaching single chain anti-BoNT/B antibodies. The Examiner then argued that it would be obvious to use the method taught by Emanuel to generate single chain antibodies against the antigen taught by Atassi *et al.* Applicants respectfully traverse.

The Examiner is reminded that *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).* Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.,* 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In the instant case, the **combination of references** cited by the Examienr fails to teach or suggest all of the elements of the presently claimed invention. Independent claim 1 is drawn to an antibody that:

> An isolated single-chain antibody that **specifically binds to an epitope specifically bound by an antibody expressed by a clone selected from the group consisting of clone S25, clone C25, clone C39, clone 1C6, and clone 1F3**, wherein said antibody binds to and **neutralizes** botulinum neurotoxin type A (BoNT/A). [emphasis added]

while independent claim 24 is drawn to:

> An isolated **single chain** anti-botulinum neurotoxin type A (anti-BoNT/A) antibody, said antibody **comprising a variable heavy (VH) complementarity determining region (CDR) listed in Table 4 (nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74)**, and wherein said antibody specifically binds to and **neutralizes** a botulinum neurotoxin type A. [emphasis added]

Independent claim 1 thus requires the **antibody bind to particular epitope** (*i.e.* the epitope(s) bound by antibodies from S25, C25, C39, or IC6), while independent claim 24 requires the antibody comprise a **VH CDR listed in Table 4**. Both claims require that the antigody be a **neutralizing antibody**.

The combination of Atassi *et al.* and Emanuel *et al.* offers no teaching or suggestion of the epitopes recited in claim 1. Similarly, the combination of Atassi *et al.* and Emanuel *et al.* offers no teaching or suggestion that the antibodies comprise the sequences recited in claim 24 or the various dependent claims. Finally, the combination of Atassi *et al.* and Emanuel *et al.* offers no teaching or suggeston that the disclosed antibodies are neutralizing antibodies. The cited combination of references thus fails to teach or suggest all of the elements of the presently claimed invention. Accordingly, the Examiner has failed to make a *prima facie* case and the rejection under 35 U.S.C. §103(a) should be withdrawn.

Moreover, in formulating his rejection, the Examiner improperly considered the method of making the claimed antibodies. In effect, the Examiner alleged that because **methods** to make single chain anti-BoNT/B antibodies, the *particular* antibodies recited in claims 1-43 would have been

obvious in light of these methods. The courts have specifically rejected this basis for rejecting claims (*see In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1994) and *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995)). In both cases, the PTO alleged that composition claims directed to nucleic acids were obvious in view of references that taught general methods for making oligonucleotides and then using them to isolate desired nucleic acids. In *Deuel*, the Federal Circuit reversed the PTO, reasoning that:

> The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. . . . **We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.** [emphasis added] *Deuel*, 51 F.3d at 1555.

Here, as in *Bell* and *Deuel*, the Examiner argues that the claimed antibodies are obvious in light of a general method for making single chain antibodies and an alleged disclosure of suitable epitopes. The Examiner has failed to show how the cited references provide any specific information about the particular claimed antibodies. To the contrary, the cited references provide no teaching or suggestion of antibodies cross-reactive with the antibodies listed in the Markush group of claim 1, or comprising the particular CDRs identified in claim 24. Furthermore, the cited art not only fails to teach or suggest antibodies having the binding specificity of the presently claimed antibodies, but also fails to teach or provide a reasonable expectation that antibodies having such particular binding specificities would also be neutralizing antibodies.

Since the cited references neither disclose nor suggest the existence of the particular claimed antibodies and the Federal Circuit has stated that consideration of a general method of discovery is an improper basis for an obviousness rejection, Applicants submit the Examiner has failed to make his *prima facie* case. Accordingly, the rejection of claims 1-43 under 35 U.S.C. §103(a) should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/144,886 WITH ENTRY OF THIS AMENDMENT

In the specification:

In the claims:

6. The antibody of claim 1, wherein said antibody comprises at least two variable heavy (VH) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74)**,

7. The antibody of claim 6, wherein said antibody comprises **[at]** three variable heavy (VH) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74)**,

8. The antibody of claim 1, wherein said antibody further comprises a variable light (VL) complementarity determining region (CDR) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74, or nucleotides 24-33, 49-55, or 88-96 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, or nucleotides 24-35, 51-57, or 99-109 of any of SEQ ID NOS: 77, 79, 91, 96, 97, or 98, or nucleotides 24-38, 54-60, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, or 92-95)**.

9. The antibody of claim 8, wherein said antibody comprises at least two variable light (VL) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74, or nucleotides 24-33, 49-55, or 88-96 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, or nucleotides 24-35, 51-57, or 99-109 of any of SEQ ID NOS: 77, 79, 91, 96, 97, or 98, or nucleotides 24-38, 54-60, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, or 92-95)**.

10. The antibody of claim 9, wherein said antibody comprises three variable light (VL) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-**

114 of any of SEQ ID NOS:51-74, or nucleotides 24-33, 49-55, or 88-96 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, or nucleotides 24-35, 51-57, or 99-109 of any of SEQ ID NOS: 77, 79, 91, 96, 97, or 98, or nucleotides 24-38, 54-60, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, or 92-95).

17. The antibody of claim 1, wherein said antibody comprises a framework region listed in Table 4 **(nucleotides 1-30, 36-49, 67-98, or 115-125 of any of SEQ ID NOS:51-74, nucleotides 1-23, 34-48, 56-87, or 97-107 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, and 90, nucleotides 1-23, 36-50, 58-89, or 99-109 of any of SEQ ID NOS:: 77, 79, 91, 96, 97, and 98, or nucleotides 1-23, 39-53, 61-92, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, and 92-95)**.

18. The antibody of claim 17, wherein said framework is a variable heavy (VH) [frame work]**framework** region listed in Table 4 **(nucleotides 1-30, 36-49, 67-98, or 115-125 of any of SEQ ID NOS:51-74)**.

19. The antibody of claim 17, wherein said framework is a variable light (VL) **[frame work]framework** region listed in Table 4 **(nucleotides 1-23, 34-48, 56-87, or 97-107 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, and 90, nucleotides 1-23, 36-50, 58-89, or 99-109 of any of SEQ ID NOS:: 77, 79, 91, 96, 97, and 98, or nucleotides 1-23, 39-53, 61-92, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, and 92-95)**.

20. The antibody of claim 18, wherein said antibody comprises at least two variable heavy (VH) framework regions listed in Table 4 **(nucleotides 1-30, 36-49, 67-98, or 115-125 of any of SEQ ID NOS:51-74)**.

21. The antibody of claim 19, wherein said antibody comprises at least two variable light (VL) framework regions listed in Table 4 **(nucleotides 1-23, 34-48, 56-87, or 97-107 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, and 90, nucleotides 1-23, 36-50, 58-89, or 99-109 of any of SEQ ID NOS:: 77, 79, 91, 96, 97, and 98, or nucleotides 1-23, 39-53, 61-92, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, and 92-95)**.

22. The antibody of claim 18, wherein said antibody comprises a variable heavy (VH) region listed in Table 4 **(SEQ ID NOS:51-74)**.

23. The antibody of claim 19, wherein said antibody comprises a variable light (VL) region listed in Table 4 **(SEQ ID NOS:75-98)**.

24. (Once amended) An isolated single chain anti-botulinum neurotoxin type A (anti-BoNT/A) antibody, said antibody comprising a variable heavy (VH) complementarity determining region (CDR) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74),** and wherein said antibody specifically binds to and neutralizes a botulinum neurotoxin type A.

25. The antibody of claim 24, wherein said antibody comprises at least two variable heavy (VH) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74)**.

26. The antibody of claim25, wherein said antibody comprises at three variable heavy (VH) complementarity determining regions (CDRs) listed in Table 4**(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74)**.

27. The antibody of claim 24, wherein said antibody further comprises a variable light (VL) complementarity determining region (CDR) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74, or nucleotides 24-33, 49-55, or 88-96 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, or nucleotides 24-35, 51-57, or 99-109 of any of SEQ ID NOS: 77, 79, 91, 96, 97, or 98, or nucleotides 24-38, 54-60, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, or 92-95)**.

28. The antibody of claim 27, wherein said antibody comprises at least two variable light (VL) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74, or nucleotides 24-33, 49-55, or 88-96 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, or nucleotides 24-35, 51-57, or 99-109 of any of SEQ ID NOS:**

77, 79, 91, 96, 97, or 98, or nucleotides 24-38, 54-60, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, or 92-95).

29. The antibody of claim 28, wherein said antibody comprises three variable light (VL) complementarity determining regions (CDRs) listed in Table 4 **(nucleotides 31-35, 50-66, or 99-114 of any of SEQ ID NOS:51-74, or nucleotides 24-33, 49-55, or 88-96 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, or nucleotides 24-35, 51-57, or 99-109 of any of SEQ ID NOS: 77, 79, 91, 96, 97, or 98, or nucleotides 24-38, 54-60, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, or 92-95)**.

36. The antibody of claim 24, wherein said antibody comprises a framework region listed in Table 4 **(nucleotides 1-30, 36-49, 67-98, or 115-125 of any of SEQ ID NOS:51-74, nucleotides 1-23, 34-48, 56-87, or 97-107 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, and 90, nucleotides 1-23, 36-50, 58-89, or 99-109 of any of SEQ ID NOS:: 77, 79, 91, 96, 97, and 98, or nucleotides 1-23, 39-53, 61-92, or 102-112 of any of SEQ ID NOS: 80, 81, 84-87, and 92-95)**.

37. The antibody of claim 36, wherein said framework is a variable heavy (VH) **[frame work]framework** region listed in Table 4 **(nucleotides 1-30, 36-49, 67-98, or 115-125 of any of SEQ ID NOS:51-74)**.

38. The antibody of claim 36, wherein said framework is a variable light (VL) **[frame work]framework** region listed in Table 4 **(nucleotides 1-23, 34-48, 56-87, or 97-107 of any of SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, nucleotides 1-23, 36-50, 58-89, or 99-109 of any of SEQ ID NOS:: 77, 79, 91, 96, 97, or 98, nucleotides 1-23, 39-53, 61-92, or 102-112 of any or SEQ ID NOS: 80, 81, 84-87, or 92-95)**.

39. The antibody of claim 37, wherein said antibody comprises at least two variable heavy (VH) framework regions listed in Table 4 **(nucleotides 1-30, 36-49, 67-98, or 115-125 of any of SEQ ID NOS:51-74)**.

40. The antibody of claim 38, wherein said antibody comprises at least two variable light (VL) framework regions listed in Table 4 **(nucleotides 1-23, 34-48, 56-87, or 97-107 of any of**

SEQ ID NOS:75, 76, 78, 82, 83, 88, or 90, nucleotides 1-23, 36-50, 58-89, or 99-109 of any of SEQ ID NOS:: 77, 79, 91, 96, 97, or 98, nucleotides 1-23, 39-53, 61-92, or 102-112 of any or SEQ ID NOS: 80, 81, 84-87, or 92-95).

41. The antibody of claim 37, wherein said antibody comprises a variable heavy (VH) region listed in Table 4 **(SEQ ID NOS:51-74)**.

42. The antibody of claim 38, wherein said antibody comprises a variable light (VL) region listed in Table 4 **(SEQ ID NOS:75-98)**.

77. The antibody of claim 1, wherein said antibody comprises a variable heavy (VH) complementarity determining region (CDR) listed in Table 4 (nucleotides 31-35, 50-66, or 99-114 of any one of SEQ ID NOS:51-74).